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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/606,129	06/28/2000	Mahin D. Maines	176/60792(6-11415-868)	5529

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EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 07/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/606,129	MAINES, MAHIN D.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *68 and 71-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *68, 71-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 68, 71-77 are pending.

Applicant's amendment of claims 68, 73, 77, cancellation of claims 69-70, submission of a new sequence listing, amendments to the specification, submission of a declaration under 37 CFR 1.132 by inventor Mahin Maines, references by Kemp et al. (TIBS 15:342-346, 1990), Shoelson et al. (Proc. Natl. Acad. Sci. 89:2027-2031, 1992), Noguchi et al. (J. Biochem. 86(4):833-848, 1979), Rigney et al. (Biochim. Biophys. Acta 957:237-242, 1988), Rigney et al. (Biochem. J. 259:709-713, 1989), Rigney et al. (Biochem. J. 255:431-435, 1988), a mouse and a pig biliverdin reductase sequence, and an alignment of human, rat, pig, and mouse biliverdin reductase sequences, in a communication filed on 3/5/2004 are acknowledged.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112, First Paragraph

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Claims 68, 71-76 remain rejected under 35 U.S.C. 112, first paragraph, new matter, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection has been discussed at length in Paper No. 16, mailed on 8/12/2003.

3. Applicants argue that the specification discloses SEQ ID NO: 16-17 as generic sequences corresponding to domains of biliverdin reductase and SEQ ID NO: 18-19, 34-35 as species of SEQ ID NO: 16-17. Furthermore, Applicants contend that the specification teaches that fragments consisting of

SEQ ID NO: 19 and 35 have been identified as inhibitors of PKC activity and fragments consisting of SEQ ID NO: 18 and 34 have been identified as enhancers of PKC activity. Thus, it is Applicant's opinion that the present application fully contemplates the use of all sequences containing the generic SEQ ID NO: 16-17 in the method claimed.

4. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the instant rejection. While is it agreed that the specification (a) discloses SEQ ID NO: 16-17 as generic sequences corresponding to domains of biliverdin reductase, (b) discloses SEQ ID NO: 18-19, 34-35 as species of the generic SEQ ID NO: 16-17, (c) discloses the inhibitory/enhancing activities of fragments consisting of SEQ ID NO: 18-19, 34-35, and (d) provides support for an *in vitro* method of regulating PKC activity with the fragments of SEQ ID NO: 18-19, 34-35, the Examiner disagrees with Applicant's contention that the method of use of fragments comprising SEQ ID NO: 16-17 as claimed is contemplated in the present application. Nowhere in the specification is there any suggestion as to the use of any fragment comprising SEQ ID NO: 16 or 17 in the method claimed, with the exception of fragments consisting of SEQ ID NO: 18-19, 34-35. The use of species of SEQ ID NO: 16-17 (i.e. SEQ ID NO: 18-19, 34-35) in the claimed method does not provide support for the use of fragments comprising the generic sequences SEQ ID NO: 16-17 in the claimed method. Thus, there is no indication that the claimed invention was within the scope of the invention as conceived by Applicants at the time the application was filed. Accordingly, Applicants are requested to cancel the new matter in response to this Office Action.

5. Claims 68, 71-77 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s),

at the time the application was filed, had possession of the claimed invention. This rejection has been discussed at length in Paper No. 16, mailed on 8/12/2003.

6. Applicants argue that the demonstration of conservation among rat and human BVR would have allowed one of skill in the art to conclude that Applicants were in possession of the claimed invention. According to Applicants, the specification discloses a representative number of species and structural or other physical and/or chemical properties. It is Applicant's contention that the evidence presented by the Examiner is indirect while the instant application presents direct evidence of the structural and functional features shared by 3 exemplary members of the recited genus. Applicants further refer to the declaration by inventor Mahin Maines (Maines declaration) and indicate that the declaration demonstrate that the structure and function of BVR proteins are highly conserved among mammalian BVR, therefore results achieved with human and/or rat BVR are predictive of results that can be achieved with other mammalian BVRs. Applicants also refer to the references by Noguchi et al. and Rigney et al. mentioned in the declaration, in support of the argument that one of skill in the art would believe that BVR is functionally well-conserved among animals.

7. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the instant rejection. The Examiner acknowledges the Maines declaration, the references submitted, and the high structural homology among four biliverdin reductases (human, pig, mouse and rat). However, the Examiner disagrees with Applicant's contention that the disclosure of ~~three~~ four mammalian biliverdin reductases and the high structural homology among them is sufficient to adequately describe a genus of biliverdin reductases which encompass a large number of proteins. It is noted that the genus "mammalian biliverdin reductases" encompasses any biliverdin reductase from any mammal and not just human, pig, mouse and rat. As shown by Applicants, one mammal may have more than one biliverdin reductase, such as in humans (SEQ ID NO: 1 and 3). Therefore, it is unclear as to how one of skill in the art can

reasonably conclude that disclosure of three biliverdin reductases is sufficient to adequately describe a genus encompassing a large number of proteins.

8. Claims 68, 71-77 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* method for regulating the activity of human protein kinase C isozymes α, β and γ with the biliverdin reductase of SEQ ID NO: 1, 3 or the peptides of SEQ ID NO: 18, 19, 34 and 35, does not reasonably provide enablement for (1) an *in vivo* method for regulating the activity of human protein kinase C isozymes α, β and γ with the biliverdin reductase of SEQ ID NO: 1, 3 or the peptides of SEQ ID NO: 18, 19, 34 and 35, or (2) an *in vivo* or *in vitro* method for regulating the activity of human protein kinase C isozymes α, β and γ with any mammalian biliverdin reductase or any fragment of a mammalian biliverdin reductase with protein kinase C regulatory activity comprising SEQ ID NO: 16-19, 34-35. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This rejection has been discussed at length in Paper No. 16, mailed on 8/12/2003.

9. Applicants argue that the specification discloses structural features required for BVR activity in Example 1. Furthermore, Applicants submit that Example 3 shows that both full length rat BVR and a fragment thereof consisting of SEQ ID NO: 18, and a fragment consisting of SEQ ID NO: 34 demonstrate PKC enhancing activity. Thus, it would be reasonable for one of skill in the art to expect that other polypeptide fragments that contain SEQ ID NO: 16 would possess similar PKC activity. Applicants indicate that *in vivo* experimental data is not a requirement for enablement of an invention. According to Applicants, the present claims do not require a particular treatment to be effected. Applicants also submit that previously submitted references (Hara et al. and Meyer et al.) show a correlation between PKC regulation in vitro and PKC regulation in vivo. Applicants refer to the

teachings of Meyer and conclude that one of skill in the art would expect other in vitro regulators of PKC activity to behave similarly in vivo.

10. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the instant rejection. The Examiner acknowledges the teachings of the specification regarding 4 specific residues in the oxidoreductase domain and the oxidoreductase motif (SEQ ID NO: 8; 8 amino acids). However, it is noted that 4 residues and a motif of 8 amino acids are very unlikely to be the only structural elements required for a protein to display biliverdin reductase activity, specially if one takes into consideration that the four mammalian biliverdin reductases provided are almost 300 amino acids long. Therefore, while some structural elements have been disclosed, the majority of the structural elements in any mammalian biliverdin reductase are unknown. In regard to arguments regarding in vivo data not being a requirement for enablement of the claimed invention, it is noted that the claims as written do not recite any limitation excluding a treatment to be effected by the claimed method. Therefore, in the absence of any limitation regarding effect, the claimed invention encompasses an in vivo method which would result in a treatment to be effected. In addition, even if the claims were to recite a limitation excluding a particular treatment as a result of the claimed method, it is reiterated herein that one of skill in the art would recognize that in vitro assays cannot be used to extrapolate in vivo results due to the increased complexity and cell-cell interactions of the in vivo environment. Freshney (Culture of Animal Cells, 1983) teaches the major differences between the in vitro and in vivo environments and how these differences may result in an environment not representative of the in vivo environment. As indicated previously, PKCs are involved in cell-surface signal transduction and their activity is highly regulated by the many interactions among different cells and interactions between the cells and the environment. The Examiner acknowledges the teachings of Hara and Meyer, however as indicated in the previous Office Action, at best, one can conclude that a staurosporine derivative shown to inhibit PKC in vitro may inhibit PKC in vivo. The inhibitors of PKC activity disclosed in the instant application, i.e. a peptide consisting

of SEQ ID NO: 19, have not been shown to be staurosporine derivatives, thus one cannot reasonably conclude that the in vivo results obtained by Meyer can be extrapolated to the claimed in vivo method.

Allowable Subject Matter

11. Claims 68, 71-77 would be allowable if claim 68 is amended to limit the scope of the claims to (1) the biliverdin reductases of SEQ ID NO: 1, 3, 4 and fragments of mammalian biliverdin reductases having protein kinase C regulatory activity comprising the peptides of SEQ ID NO: 18-19, 34-35, and (2) *in vitro*.

Conclusion

12. No claim is in condition for allowance.

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

14. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 872-9306. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be

retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

15. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
July 7, 2004

REBECCA E. PRESTY
PRIMARY EXAMINER
GROUP ~~1600~~ 1600